SUMMARY of SAFETY and EFFECTIVENESS DATA
MOSAIC® PORCINE BIOPROSTHESIS

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1. General Information

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	MOSAIC® Porcine Bioprosthesis
Applicant's Name and Address:	Medtronic Heart Valves 1851 East Deere Avenue Santa Ana, CA 92705
PMA Application Number	P990064
Date of Panel Recommendation	N/A
Date of Notice of Approval to the Applicant	JUL 14 2000

2. Indications for Use

The MOSAIC® Porcine Bioprosthesis (Models 305 and 310) is indicated for the replacement of malfunctioning native or prosthetic aortic and mitral heart valves.

3. Device Description

The MOSAIC® Porcine Bioprosthesis (Model 305, Aortic and Model 310, Mitral) is comprised of a porcine aortic valve which has been crosslinked and preserved in buffered 0.2% glutaraldehyde solution. During fixation, hydrostatic pressure is applied to the porcine aortic root while a zero pressure differential is maintained across the valve leaflets (Physiologic Fixation™).

The fixed aortic root is fitted and secured to a cloth covered flexible acetyl homopolymer stent. All stitching is done with polyester suture. The MOSAIC®Porcine Bioprosthesis is treated with the AOA® process* which uses alpha-amino oleic acid (AOA), a compound derived from oleic acid, a naturally occurring long-chain fatty acid. The MOSAIC® Porcine Bioprosthesis is supplied sterile in a buffered 0.2% glutaraldehyde solution.

***No clinical data are available which evaluate the long-term impact of the AOA treatment in patients.**

AOA® is a registered trademark of Biomedical Design, Inc., Atlanta, Georgia.

The MOSAIC® Porcine Bioprostheses are designed for both the aortic position (Model 305) and the mitral position (Model 310). They are available in the following diameters:

Model 305: 21 mm, 23 mm, 25 mm, 27 mm, and 29 mm
Model 310: 25 mm, 27 mm. 29 mm, and 31 mm

The stents of both the aortic and mitral models are constructed from acetal homopolymer and covered with polyester fabric. The stents have a slightly lower profile (approximately 2 mm) for all bioprosthesis sizes as compared to the Hancock Standard Bioprosthesis and the Hancock Modified Orifice Bioprosthesis.

The inflow edge of the stent of the aortic bioprosthesis is scalloped, as is the sewing ring. The sewing ring is mounted flush with the inflow edge of the stent. This facilitates implantation in either the supra-annular or intra-annular position. If the supra-annular position is preferred, the entire bioprosthesis can be seated superior to the annulus, allowing the use of a larger MOSAIC® Porcine Bioprosthesis aortic valve. The inflow edges of the mitral bioprosthesis stent and sewing ring are flat. The mitral sewing ring contains polyester felt, allowing for easy needle penetration and low suture drag.

To allow radiographic visualization, both the aortic and mitral stents are fitted with stent post markers. The stent post markers are placed close to the apex of each stent post to allow visualization of the orientation of the posts to the aortic and ventricular walls.

Disposable acetal homopolymer holders are sutured to both the aortic and mitral bioprostheses. In the case of the mitral bioprosthesis, the suture attaching the bioprosthesis holder prevents the looping of the surgeon's sutures during implantation. The mitral valve holder has a ratcheting mechanism to slightly draw in the stent post tips which facilitates the insertion of the bioprosthesis into the patient's mitral annulus. The disposable holders are designed to fit the reusable Medtronic Handle (Model 0791). The handle is equipped with a knurled locknut to allow the bioprosthesis to be oriented and secured in a given position with respect to the handle. The handle is also used with the MOSAIC® Porcine Bioprosthesis valve obturators for measuring the annulus.

4. Contraindications

None known

5. Warnings and Precautions

FOR SINGLE USE ONLY.

DO NOT RESTERILIZE the valve by any method. Exposure of the MOSAIC® Porcine Bioprosthesis and container to irradiation, steam, ethylene oxide, or chemical sterilization will render the bioprosthesis unfit for use.

WARNING: Accelerated deterioration due to calcific degeneration of bioprostheses may occur in:

- children, adolescents, or young adults.
- patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism).

Precautions Prior to Use

Do not use the MOSAIC® Porcine Bioprostheses:

- if the tamper evident seal is broken.
- if the glutaraldehyde storage solution does not completely cover the bioprosthesis.
- if the bioprosthesis has been exposed to freezing or has had prolonged exposure to heat.
- if the bioprosthesis is damaged.

Precautions During Use

- Do not expose the bioprosthesis to solutions other than the storage solution in which it was shipped, the sterile isotonic saline solution used during the rinsing procedure, or the sterile isotonic saline solution used to irrigate the bioprosthesis.
- Do not allow the tissue of the bioprosthesis to dry. Continuous submersion or irrigation is required.
- Do not add antibiotics to either the storage or the rinse solution. Do not apply antibiotics to the bioprosthesis.
- Do not lacerate the tissue. If a bioprosthesis is damaged, it must be explanted and replaced.
- Do not attempt to repair a damaged bioprosthesis.
- Do not use cutting needles, as they may cause structural damage to the fabric of the bioprosthesis.
- Passing a catheter, surgical instrument or transvenous pacing lead through the bioprosthesis may damage the bioprosthesis and is, therefore, not recommended.
- Trim suture ends close to the knot to prevent abrasion of leaflet tissue.
- When selecting a valve size, consideration of the cardiac anatomy is necessary, and care must also be taken to select a bioprosthesis which adequately provides for the hemodynamic requirements of the patient.

Aortic Valve Replacement

- Select a bioprosthesis which will fit snugly in the aortic root or annulus. Do not attempt to insert too large a valve.
- Orient the stent posts and seat the bioprosthesis so that there is not obstruction to the coronary ostia.

Mitral Valve Replacement

- Select a bioprosthesis which can accommodate the size and configuration of the ventricle and the mitral annulus.
- The bioprosthesis should be oriented so that the largest intercommissural space corresponds with patient's left ventricular outflow tract. From the atrial aspect of the prosthesis, the largest intercommissural space lies between the green suture marker on the sewing ring and the first commissure in the counter-clockwise direction. Proper positioning in the mitral annulus may be approximated by orienting the green suture marker on the atrial aspect of the sewing ring in the direction of the lateral fibrous trigone. This orientation may minimize the potential for obstruction to the aortic outflow.
- Maintain suture tension when lowering the bioprosthesis into the mitral annulus to prevent suture entanglement with the stent posts. Examine the ventricular aspect of the bioprosthesis to verify a suture has not been looped around the stent posts.
- Special care should be exercised when implanting a bioprosthesis in the mitral position in a patient with a small left ventricle. Adequate clearance must be available to avoid contact between the prosthesis stent post and the ventricular wall. Repeated contact between these structures could result in perforation of the ventricular wall.

6. Alternative Practices and Procedures

The alternative to the MOSAIC® Porcine Bioprosthesis is surgical replacement of the malfunctioning aortic or mitral valve with a commercially available homograft, mechanical prosthetic valve, stentless valve, or stented bioprosthetic heart valve. The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

Other forms of treatment may include the use of cardiac drug therapy.

7. Marketing History

Commercial distribution of the MOSAIC® Porcine Bioprosthesis outside the U.S. began in 1997. Currently the bioprosthesis is distributed in Argentina, Australia, Austria, Belgium, Canada, Columbia, France, Germany, Italy, Japan, Netherlands, New Zealand, Norway, Singapore, Spain, Switzerland, England, Scotland, Ireland and Wales.

The MOSAIC ®Porcine Bioprosthesis has never been withdrawn from distribution for any reason associated with the safety and/or the effectiveness of the device.

8. Adverse Events

A prospective, nonrandomized, multi-center clinical study was conducted to assess the safety and performance of the MOSAIC® Porcine Bioprosthesis. Patients were evaluated preoperatively, within 30 days postoperative, 3-6 months postoperative, at one year (11-14 months) postoperative, and annually thereafter. Patients were monitored throughout the postoperative period for possible adverse events. One thousand two hundred fifty-two (1252) patients had isolated aortic valve replacement (AVR) and 365 patients had isolated mitral valve replacement (MVR). Mortality and valve-related morbidity rates after implantation with the MOSAIC® Porcine Bioprosthesis are summarized in the tables below. There was an insufficient number of patients receiving the 33mm mitral valve size to evaluate effectiveness, however, the data from the 9 patients of this size have been included in the following for safety data.

Observed Adverse Events -- Isolated Aortic Valve Replacement (AVR)

The adverse event rates were based on 1252 bioprostheses implanted in 1252 patients at 17 centers. The cumulative follow-up was 2745.3 patient-years with a mean follow-up of 2.2 years (SD=1.2 years, range=0 - 5.2 years).

Table 1: Observed Adverse Event Rates for AVR

All patients analyzed: N=1252 Cumulative follow-up=2745.3 patient-years

	Early Events[1]		Late Events[2]		Freedom From Event (%) [95% CI][3]			
	n	% of Patients	n	%/Pt.-Yr.	1 Year	2 Years	3 Years	4 Years
All Deaths	41	3.3	82	3.1	93.7 [92.3, 95.2]	91.9 [89.9, 93.8]	88.6 [85.5, 91.7]	85.6 [79.0, 92.1]
Valve-Related or Unexplained	4	0.3	24	0.9	98.7 [98.0, 99.4]	98.2 [97.2, 99.1]	97.1 [95.3, 98.8]	96.5 [92.9, 100.0]
Valve-Related Adverse Events								
Primary Thromboembolism[4]	19	1.4	33	1.25	96.9 [95.8, 98.0]	96.3 [94.9, 97.7]	95.6 [93.5, 97.7]	95.6 [91.5, 99.7]
Permanent Neurological Event	7	0.6	13	0.5	98.7 [98.1, 99.4]	98.4 [97.5, 99.3]	98.0 [96.6, 99.5]	98.0 [95.3, 100.0]
Transient Neurological Event[4]	12	0.9	20	0.8	98.1 [97.2, 98.9]	97.8 [96.8, 98.9]	97.5 [95.9, 99.1]	97.5 [94.3, 100.0]
Primary Valve Thrombosis	0	0.0	5	0.2	99.7 [99.4, 100.0]	99.6 [99.2, 100.0]	99.4 [98.7, 100.0]	99.4 [98.0, 100.0]
Structural Valve Deterioration[5]	0	0.0	1	0.0	100.0	100.0	100.0	100.0
Nonstructural Valve Dysfunction	0	0.0	4	0.15	99.7 [99.4, 100.0]	99.7 [99.4, 100.0]	99.7 [99.2, 100.0]	99.1 [97.3, 100.0]
Leaflet Dysfunction	0	0.0	1	0.0	100.0	100.0	100.0	99.4 [97.8, 100.0]
Patient Prosthesis Mismatch	0	0.0	3	0.1	99.7 [99.4, 100.0]	99.7 [99.4, 100.0]	99.7 [99.2, 100.0]	99.7 [98.7, 100.0]
Endocarditis	1	0.1	19	0.7	99.3 [98.8, 99.8]	98.7 [97.9, 99.5]	97.7 [96.2, 99.2]	97.4 [94.3, 100.0]
All Primary Paravalvular Leak	6	0.5	13	0.5	99.1 [98.5, 99.7]	98.4 [97.5, 99.3]	98.3 [96.9, 99.6]	98.3 [95.7, 100.0]
Major Primary Paravalvular Leak	1	0.1	2	0.1	99.8 [99.4, 100.0]	99.8 [99.4, 100.0]	99.8 [99.2, 100.0]	99.8 [98.8, 100.0]
All Antithromboembolic-Related Hemorrhage	23	1.8	28	1.1	96.5 [95.4, 97.6]	96.3 [94.9, 97.7]	95.3 [93.2, 97.5]	95.3 [91.1, 99.5]
Major Antithromboembolic-Related Hemorrhage	15	1.2	20	0.8	97.6 [96.6, 98.5]	97.5 [96.3, 98.6]	96.5 [94.6, 98.4]	96.5 [92.9, 100.0]
Primary Hemolysis	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Reoperation	0	0.0	20	0.8	99.2 [98.7, 99.8]	99.0 [98.3, 99.7]	98.4 [97.2, 99.7]	95.7 [91.7, 99.6]
Explant	0	0.0	19	0.7	99.3 [98.8, 99.8]	99.1 [98.4, 99.8]	98.5 [97.3, 99.8]	95.8 [91.8, 99.7]

Notes:

1. Early deaths occurred within 30 days of implant if the patient was discharged from the hospital, or at any time after implant if the patient was not discharged from the hospital. Early valve-related adverse events occurred within the first 30 days of implant. Early event rates were calculated as the percentage of patients.
2. Late deaths occurred after 30 days postoperative, if the patient was discharged from the hospital. Late valve-related adverse events occurred after 30 days postoperative. Late event rates were calculated as linearized rates (%/patient-year). Calculations for late death rates were based on 2642.5 late patient-years. Calculations for late valve-related adverse event rates were based on 2645.2 late patient-years.
3. Freedom from event (early or late) rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard error of the Kaplan-Meier estimate for the confidence interval for adverse events with at least one occurrence.
4. Two early events occurred in one patient.
5. The adverse event occurred after four years postoperative.

Observed Adverse Events -- Isolated Mitral Valve Replacement (MVR)
The adverse event rates were based on 365 bioprostheses implanted in 365 patients at 17 centers. The cumulative follow-up was 644.2 patient-years with a mean follow-up of 1.8 years (SD=1.3 years, range=0 - 5.2 years).

Table 2: Observed Adverse Event Rates for MVR
All patients analyzed: N=365 Cumulative follow-up=644.2 patient-years

	Early Events[1]		Late Events[2]		Freedom From Event (%) [95% CI][3]			
	n	% of Patients	n	%/Pt.-Yr.	1 Year	2 Years	3 Years	4 Years
All Deaths	15	4.1	25	4.1	92.5 [89.2, 95.7]	89.9 [85.3, 94.5]	85.9 [78.7, 93.0]	80.0 [66.2, 93.7]
Valve-Related or Unexplained	2	0.5	8	1.3	98.4 [96.8, 100.0]	97.3 [94.7, 99.9]	96.4 [92.3, 100.0]	92.2 [82.2, 100.0]
Valve-Related Adverse Events								
Primary Thromboembolism[4]	13	3.0	10	1.6	95.1 [92.3, 97.8]	93.9 [90.0, 97.8]	93.9 [88.5, 99.3]	92.2 [82.0, 100.0]
Permanent Neurological Event	4	1.1	2	0.3	98.6 [97.1, 100.0]	98.6 [96.7, 100.0]	98.6 [96.0, 100.0]	97.0 [90.5, 100.0]
Transient Neurological Event[4]	9	1.9	8	1.3	96.5 [94.1, 98.8]	95.3 [91.9, 98.8]	95.3 [90.5, 100.0]	95.3 [87.1, 100.0]
Primary Valve Thrombosis	0	0.0	1	0.2	100.0	100.0	100.0	98.5 [93.8, 100.0]
Structural Valve Deterioration	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Nonstructural Valve Dysfunction	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Leaflet Dysfunction	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Patient Prosthesis Mismatch	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Endocarditis	2	0.5	6	1.0	98.2 [96.6, 99.9]	98.2 [96.1, 100.0]	98.2 [95.3, 100.0]	95.9 [88.4, 100.0]
All Primary Paravalvular Leak	3	0.8	9	1.5	96.9 [94.7, 99.1]	96.4 [93.4, 99.4]	95.3 [90.7, 100.0]	95.3 [87.1, 100.0]
Major Primary Paravalvular Leak	0	0.0	3	0.5	99.7 [99.0, 100.0]	98.6 [96.7, 100.0]	98.6 [96.0, 100.0]	98.6 [94.1, 100.0]
All Antithromboembolic-Related Hemorrhage	7	1.9	11	1.8	95.8 [93.3, 98.4]	95.3 [91.9, 98.7]	93.4 [87.9, 98.9]	91.0 [80.3, 100.0]
Major Antithromboembolic-Related Hemorrhage	5	1.4	7	1.1	97.3 [95.2, 99.4]	96.7 [93.9, 99.6]	94.8 [89.9, 99.7]	94.8 [86.5, 100.0]
Primary Hemolysis	0	0.0	0	0.0	100.0	100.0	100.0	100.0
Reoperation	0	0.0	5	0.8	99.3 [98.3, 100.0]	98.8 [97.0, 100.0]	98.8 [96.4, 100.0]	94.9 [86.6, 100.0]
Explant	0	0.0	5	0.8	99.3 [98.3, 100.0]	98.8 [97.0, 100.0]	98.8 [96.4, 100.0]	94.9 [86.6, 100.0]

Notes:
1. Early deaths occurred within 30 days of implant if the patient was discharged from the hospital, or at any time after implant if the patient was not discharged from the hospital. Early valve-related adverse events occurred within the first 30 days of implant. Early event rates were calculated as the percentage of patients.
2. Late deaths occurred after 30 days postoperative, if the patient was discharged from the hospital. Late valve-related adverse events occurred after 30 days postoperative. Late event rates were calculated as linearized rates (%/patient-year). Calculations for late death rates were based on 614.1 late patient-years. Calculations for late valve-related adverse events were based on 615.2 late patient-years.
3. Freedom from event (early or late) rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard error of the Kaplan-Meier estimate for the confidence interval for adverse events with at least one occurrence.
4. Two early events occurred in each of two patients.

Potential Adverse Events
Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include:

- cardiac dysrhythmias
- death
- endocarditis
- hemolysis
- hemorrhage, anticoagulant/antiplatelet-related
- leak, transvalvular or paravalvular
- nonstructural dysfunction (pannus, suture dehiscence, inappropriate sizing, or other)
- structural deterioration (calcification, leaflet tear, or other)
- thromboembolism
- valve thrombosis

9. Summaries of Nonclinical Studies
9.1 Bench Testing
9.1.1 Biocompatibility, Immunology and Toxicology

COMPONENTS

The acetyl homopolymer stent material, polyester fabric and polyester suture were subjected to acute systemic toxicity, intracutaneous toxicity and cytotoxicity testing. All test results were found acceptable. The MOSAIC® Porcine Bioprosthesis also contains eyelet markers of Haynes Alloy #25 at the distal aspect of each commissure post.

Biocompatibility tests were performed on alpha amino oleic acid (AOA) and glutaraldehyde tanned porcine tissue treated with AOA. All samples used in these tests were subjected to the maximum number of resterilization cycles (2X) with the exception of the testing of the AOA compound. The biocompatibility of the AOA compound and the AOA-treated tissue were assessed by determining its influence on the inflammatory response, cytotoxicity, hemolysis, mutagenicity (Ames genotoxicity), USP rabbit pyrogenicity, systemic toxicity, intracutaneous toxicity, sensitization (Kligman guinea pig) and thrombogenicity.

FINISHED PRODUCT

The biocompatibility of finished, sterile clinical quality MOSAIC® Porcine Bioprostheses was assessed by determining its influence on inflammatory response, sensitization (Kligman guinea pig), cytotoxicity, systemic toxicity, intracutaneous toxicity, thrombogenicity, pyrogenicity (USP rabbit and LAL methods), hemolysis, muscle implantation, and mutagenicity (Ames).

A health risk assessment was done to assess the amount of glutaraldehyde that leaches out over time from the AOA-treated tissue. All tests were negative, and the amount of glutaraldehyde leaching out was 0.069 mg/l, which peaked at 4 hours, and was less than the 20.5 mg/l used in the acute toxicity test.

Carcinogenicity, subchronic, chronic and reproductive toxicity testing was not conducted because glutaraldehyde tanned porcine tissue has a long history of use, the device does not contact soft tissue, and no leachable components were detected during acute testing.

The approach used for the biocompatibility assessment of the MOSAIC®Porcine Bioprosthesis is consistent with the intent of the Biological Evaluation of Medical Devices Memorandum (G95-

1) issued by FDA on May 1, 1995. The results of the biocompatibility studies performed support the biocompatibility of the MOSAIC® Porcine Bioprosthesis.

9.1.2 Hydrodynamic Performance

Testing was conducted to provide an assessment of the hydrodynamic performance of the MOSAIC® Porcine Bioprosthesis as compared to the Hancock Porcine Bioprosthesis (Standard) control valve. All MOSAIC® Porcine Bioprosthesis and control valves used in these tests were final production models subjected to the recommended maximum number of resterilization cycles using the worst-case conditions.

The data obtained from hydrodynamic testing of the MOSAIC® Porcine Bioprostheses showed steady and pulsatile flow gradients that were lower than control valve gradients; pulsatile flow leakage volumes and dynamic regurgitation data were similar for the MOSAIC and the control valves, and MOSAIC® Porcine Bioprosthesis exhibited improved forward flow characteristics as compared to the Hancock control valve.

Results of the verification of the Bernoulli relationship indicate that the Bernoulli relationship $\Delta P = 4(V_2^2 - V_1^2)$ may be used to noninvasively assess pressure gradients in patients implanted with the MOSAIC Porcine Bioprosthesis.

Hydrodynamic performance test results are summarized in Table 3.

Table 3: Hydrodynamic Performance Testing and Results

Steady Flow Pressure Drop	3 each size & type	1 – 25 mm Aortic 1 – 29 mm Mitral	**Flow rates** = 5,10,15,20,25,30 L/min (accuracy = ± 1.0 mmHg)	Pressure drop ≤ control valve	Pass
Pulsatile Flow Pressure Drop	3 each size & type	1 – 25 mm Aortic 1 – 29 mm Mitral	**Cardiac output range** = 2.5 to 7.5 L/min (accuracy = ±1.0 mmHg) **Pulse rate** = 70 bpm w/systole accounting for ~ 35% of simulated cardiac cycle	Pressure drop ≤ control valve	Pass
Pulsatile Flow Leakage	3 each size & type	1 – 25 mm Aortic 1 – 29 mm Mitral	**Simulated heart rate** = 70 bpm **Cardiac output** = 5.0 L/min **Aortic Valve:** mean arterial pressure: 90, 110,130 & 150 mmHg **Mitral Valve:** mean left ventricular pressure: 40,50,70 & 80 mmHg	Leakage volume ≤ control valve	Pass
Dynamic Regurgitation (Leakage Volume vs Back Pressure)	3 each size & type	1 – 25 mm Aortic 1 – 29 mm Mitral	**Beat rates** = 50,70,100 bpm **Cardiac outputs** = 2.5,4.5,6.5 L/min, Accuracy = ± 1 ml/beat	Regurgitant volume ≤ control valve of equivalent flow area	Pass
In Vitro Doppler Ultrasound	1 each: 21,25,29 mm Aortic 25,29,33 mm Mitral	N/A	**Cardiac outputs** = 2.5 to 8.0 L/min **Pulse rate** = 70 bpm **Systolic duration** = 280 to 320 msec **Mean aortic pressure** = 90 to 100 mmHg **Mean left atrial pressure** = 5 to 10 mmHg	Assessment: Determine if the Bernoulli equation: $\Delta P = 4(V_2^2 - V_1^2)$ may be used to assess peak and mean pressure gradients	Bernoulli equation works well within the experimental error (5%)
Flow Visualization (Color Doppler Flow Mapping)	1 – 27 mm Aortic 1 – 27 mm Mitral	N/A	Pulsatile Flow Conditions	Qualitatively visualize leaflet motion and downstream flow fields	Improved forward flow characteristics as compared to control

Note: N/A = not applicable

9.1.3 Structural Performance

Testing was conducted to evaluate the structural performance of the MOSAIC® Porcine Bioprosthesis. The tests included accelerated wear, fatigue, dynamic failure mode, stent creep, stent deflection, stent absorption and adsorption. The results of the structural performance tests are summarized in Table 4.

Table 4: Structural Performance Tests

Accelerated Wear	**Test:** 6 – 29 mm Aortic 6 – 33 mm Mitral 3 - each all other Size and Type **Hancock Std.** **Control:** 1-29 mm Aortic 1-33 mm Mitral	Test and control valves to exhibit similar results at end of test	All valves functioned normally, exhibiting proper opening and closing and maintained closed-valve pressure drop throughout the test. No valve exhibited evidence of change in co-aptation or cusp shape. No valve exhibited any evidence of delamination or alteration of leaflet structure.
Fatigue-Delrin Material Tensile Properties	12 samples per ASTM D638	Assessment: Determine material constants of acetyl homopolymer	No abnormalities were observed during testing. The results of this test were used for finite element analysis.
Fatigue-Finite Element Stress Analysis	Each size and type	Assessment: Determine 1) the maximum stresses which result from deflections of stent posts toward the center of the valve and 2) the effect of manufacturing tolerances on stress distribution	The maximum tensile stress in the aortic stents with nominal dimensions was 2850 psi. The largest compressive stress was 3690 psi. The maximum tensile stress for mitral valves with nominal dimensions was 2240 psi and the largest compressive stress was 3580 psi.
Fatigue Lifetime Analysis	3 each size and type	Assessment: Define the fatigue resistance of the MOSAIC stents	None of the 30 stents experienced failure. Scanning electron microscopy showed no sign of fatigue cracks in any of the 30 stents. Statistical analysis showed 95% confidence that 90% of stents loaded to 4600 psi will survive 6E8 cycles of fatigue.
Dynamic Failure Mode	**Test:** 1 each size and type **Hancock Std.** **Control:** 1-29 mm Aortic 1-33 mm Mitral	Assessment: Determine the ultimate failure mode of the MOSAIC valve	Three MOSAIC valves experienced tissue failure and seven failed from loss of co-aptation due to excessive stent post deflection. None of the valves experienced premature failure and all valves performed to at least 2.5 times the hypertensive pressure of 200 mmHg.

Table 4: Structural Performance Tests (Continued)

Sewing Ring Integrity	N/A	Assessment: Determine mechanical integrity of the sewing ring	The method and cloth material used for constructing the sewing ring are based upon the Medtronic Hancock I and Hancock Modified Orifice bioprostheses. The integrity of the sewing ring is well established in the clinical history of the predicate products; therefore, additional testing was not deemed necessary.
Stent Creep	10-27 mm stents 5 @ 1± 0.02 Hz 5 @ 10 ± 2 Hz	Assessment: Determine dynamic creep characteristics of the MOSAIC stent	Creep stabilization occurred in less than two weeks. No tertiary creep was observed.
Stent Deflection	60 valves, 6 each size and type	Assessment: Determine stent post deflection with respect to transvalvular pressure drop	No abnormalities were observed during the test. In 58/60 valves tested, the highest deflection at 200 mmHg was observed at the LR commissure and 9 of the 10 size groups exhibited the highest deflection at the LR commissure.
Absorption and Adsorption	10 - 1.5" disks per time point 10 - 33 mm stents	Assessment: Determine absorption and adsorption properties of the MOSAIC stent when exposed to aqueous physiological solutions	Acetyl homopolymer is suitable for use in physiological environments.
Supporting Structural Testing	As defined in specific test procedures	Assessment: Use Hancock II stent *in vitro* test data to support MOSAIC data relative to Fatigue-Delrin Material Properties, Fatigue-Fracture Mechanics, Fatigue-Finite Element Analysis, Fatigue Lifetime Analysis, Dynamic Failure Mode, Stent Creep, and Stent Deflection	The results of the testing for the Hancock II stent support the results of the testing performed on the MOSAIC stent.

Note: N/A = not applicable

9.2 Animal Studies

Three *in vivo* implant studies (chronic) were conducted on the MOSAIC® Porcine Bioprosthesis in the juvenile sheep model. All three studies utilized 25 mm MOSAIC® Porcine Bioprosthesis (AOA-treated and non-AOA-treated) and Medtronic Hancock I control valves implanted in the orthotopic position. All were long-term (chronic) studies performed to evaluate the performance and handling characteristics of the MOSAIC® Porcine Bioprosthesis. In addition, the studies were conducted to evaluate the effectivity of AOA® as a potential antimineralization treatment.

The findings of the initial study (Study 1) were inconclusive due to the lack of statistical analysis and the observation that the MOSAIC® Porcine Bioprostheses without AOA treatment demonstrated similar quantitative calcium levels as AOA treated bioprostheses. The animal model was validated by the observation that the control Hancock I valves demonstrated a marked increase in leaflet calcium content.

AOA® Effectiveness:
Studies II and III demonstrated a statistically significant reduction in leaflet tissue calcification in the AOA-treated MOSAIC group in comparison to nontreated MOSAIC valves. In addition, a statistically significant reduction in leaflet calcification was demonstrated in Study II in the AOA-treated MOSAIC group in comparison to the Hancock I controls. In Study III, too few Hancock I control animals survived full term to determine a statistically significant difference. A reduction in aortic wall calcification was also demonstrated in these studies; however, the reduction may not be biologically significant.

Clinical Chemistry and Hematology:
For all studies, the chemical and hematological parameters were within normal range.

Histopathology:
For all studies, histopathological findings were as anticipated in explanted porcine bioprostheses from mitral valve juvenile sheep studies. The gross pathological evaluation in this series of explants indicated a higher than anticipated incidence of small fibrin thrombi on the leaflets surface of both treated and control groups.

Hemodynamics:
Study II: The incidence and severity of regurgitation was significantly less in the MOSAIC group as compared to the control group. Pulmonary artery systolic pressure was also significantly less in the MOSAIC group as compared to the control group. No statistically significant difference in mean diastolic gradient was detected. Effective orifice area (EOA) for the MOSAIC valve was 1.74 cm^2. EOA for the control group could not be determined due to the extent of regurgitation.

Study III: The pressure gradient was significantly less ($p=0.01$) in the AOA-treated MOSAIC group (6.47 mmHg ± 3.93 mmHg) in comparison to the control group (19.27 mmHg ± 2.03 mmHg). Flow (L/min) was similar across all groups. ANOVA (analysis of variance methods) indicated a smaller average EOA in the non-AOA-treated MOSAIC and control groups as compared to the treated MOSAIC group. On ventriculography, no groups exhibited evidence of regurgitation and all groups appeared to function normally.

Handling Characteristics:
For all studies, surgical handling and implantation characteristics were noted to be comparable to other stented bioprostheses.

Additional Animal Studies
A fourth *in vivo* animal study, originally conducted with the objective of evaluating a manufacturing process improvement was also considered for evaluation of the safety and performance of the MOSAIC® Porcine Bioprosthesis. This study also utilized 25 mm MOSAIC mitral valves implanted in the orthotopic position in the juvenile sheep model and provided data relevant to the evaluation of the MOSAIC valve. The results of this study are similar to those reported in Studies II and III.

In addition to the sheep studies, a series of subdermal rat implant studies were performed, utilizing treated (AOA) and nontreated samples. The implant duration was 1,2,3, and 4 months. For the period of time studied, the AOA treated samples contained significantly less calcium (mg of calcium/mg dry tissue) than the untreated samples.

9.3 Sterilization

The MOSAIC® Porcine Bioprosthesis is sterilized in a 0.2% buffered glutaraldehyde solution with placement of the packaged valve assembly into an incubator for terminal sterilization at 38°C - 42°C for 20-24 hours. After completion of terminal sterilization the product is held in quarantine until sterility is verified in accordance with process specifications. Annual requalification of the sterilization process is performed.

9.4 Shelf Life

The shelf life for the MOSAIC® Porcine Bioprosthesis underwent qualification testing to ensure that both package and product integrity had been maintained after aging to three years. The package integrity samples were exposed to accelerated aging to three years, whereas the product integrity samples underwent real-time aging to a minimum of three years.

9.4.1 Package Integrity

The package integrity for the MOSAIC® Porcine Bioprosthesis was qualified for a three-year shelf life through package integrity testing conducted for the FREESTYLE Aortic Root Bioprosthesis. This testing is directly applicable to MOSAIC bioprostheses since the jar/lid/seal assembly is identical for the two product lines. The FREESTYLE package assembly, which includes the bioprosthesis within a retainer, is considered worst-case. The FREESTYLE bioprosthesis retainer has a greater mass (~42g for FREESTYLE versus ~15g for MOSAIC) and thus can be concluded to have a greater impact on the jar/lid/seal assembly during shipping/handling.

Testing included a vacuum leak test, lid removal torque test, solution volume check test, and a microbial challenge. All test samples were subjected to worst-case processing conditions for sterilization of three cycles (maximum manufacturing specification of two cycles plus one additional cycle) and environmental stress conditioning. In addition, samples underwent a shipping and handling test prior to performance of the sterile barrier tests.

9.4.2 Product Integrity

The shelf life for the MOSAIC® Porcine Bioprosthesis was qualified by testing to ensure that product integrity had been maintained after real-time aging to three years. Product integrity

testing included a battery of tests that were designed to affirm the functionality of the valve through examination of multiple aspects of valve performance and structure. The qualification included shrink temperature, collagen content (enzyme susceptibility), moisture content, hydrodynamic performance, histological evaluation, storage solution pH and glutaraldehyde percentage. All three-year real-time aged samples were sterilized three times (the maximum allowed per manufacturing specifications) and underwent environmental stress conditioning prior to performing the product integrity assessment.

Results revealed that the established criteria for the package and product integrity testing were met. Therefore, the MOSAIC® Porcine Bioprosthesis is considered to be qualified for a three-year shelf life.

AOA Effectiveness:

The AOA treatment applied to the MOSAIC® Porcine Bioprosthesis was evaluated for efficacy over time. The testing consisted of anticalcification studies (i.e., subdermal implants in rats) performed on MOSAIC bioprosthesis tissue held for real-time shelf life aging and analysis of storage solution pH over time. Test results indicate that the AOA treatment remains effective over the shelf life period of 36 months and the storage solution pH remains within acceptable ranges.

10. Summary of Clinical Studies

The safety endpoints in this study were mortality and valve-related morbidity. The effectiveness endpoints in this study were New York Heart Association (NYHA) functional classification and hemodynamic assessments obtained by echocardiography. Patient demographic data and effectiveness data are summarized in the tables below.

Table 5: Patient Characteristics: AVR
All patients analyzed: N=1252

Age at implant in years (mean ± SD, N [min., max.])	70 ± 8, 1252 [21, 89]
Gender (% male / % female)	64% / 36%
Etiology	
Stenosis- % of pts. with stenosis alone (% (number in subgroup/N))	67% (842/1252)
Insufficiency- % of pts. with insufficiency alone (% (number in subgroup/N))	11% (141/1252)
Mixed-% of pts. with stenosis and insufficiency (% (number in subgroup/N))	21.5% (269/1252)

Table 6: Patient Characteristics: MVR
All patients analyzed: N=365

Age at implant in years (mean ± SD, N [min., max.])	68 ± 11, 365 [17, 84]
Gender (% male / % female)	47% / 53%
Etiology	
Stenosis- % of pts. with stenosis alone (% (number in subgroup/N))	10% (38/365)
Insufficiency- % of pts. with insufficiency alone (% (number in subgroup/N))	76% (279/365)
Mixed-% of pts. with stenosis and insufficiency (% (number in subgroup/N))	13% (48/365)

Table 7: Effectiveness Outcomes, Functional NYHA: AVR
All patients analyzed: N=1252, percent (numerator/N)

Endpoint	Preoperative	3-6 Months	1 Year	3 Years
Functional NYHA				
I- % of pts. in NYHA class I	2% (30/1252)	75% (865/1150)	74.5% (812/1090)	58% (287/498)
II- % of pts. in NYHA class II	25% (311/1252)	23% (266/1150)	24% (261/1090)	41% (202/498)
III- % of pts. in NYHA class III	58.5% (732/1252)	1% (17/1150)	1.5% (16/1090)	2% (9/498)
IV- % of pts. in NYHA class IV	14% (179/1252)	0% (2/1150)	0% (1/1090)	0% (0/498)

Table 8: Effectiveness Outcomes, Functional NYHA: MVR
All patients analyzed: N=365, percent (numerator/N)

Endpoint	Preoperative	3-6 Months	1 Year	3 Years
Functional NYHA				
I- % of pts. in NYHA class I	1% (2/363)	59% (190/322)	62% (161/260)	55% (56/101)
II- % of pts. in NYHA class II	20% (74/363)	37% (119/322)	34% (88/260)	39% (39/101)
III- % of pts. in NYHA class III	59% (213/363)	3% (11/322)	3.5% (9/260)	5% (5/101)
IV- % of pts. in NYHA class IV	20% (74/363)	1% (2/322)	1% (2/260)	1% (1/101)

Table 9: Effectiveness Outcomes, Hemodynamics, Valvular Regurgitation: AVR
All patients analyzed: N=1252, percent (numerator/N)

Endpoint	≤30 Days	3-6 Months	1 Year	3 Years
Valvular Regurgitation				
% of pts. with no regurgitation	79% (958/1207)	76% (882/1153)	75% (824/1094)	77% (378/490)
% of pts. with trivial regurgitation	13% (155/1207)	15% (172/1153)	16% (175/1094)	15% (73/490)
% of pts. with mild regurgitation	7% (85/1207)	7% (85/1153)	7% (79/1094)	6% (30/490)
% of pts. with mod regurgitation	1% (9/1207)	1% (12/1153)	1% (14/1094)	2% (9/490)
% of pts. with mod severe regurgitation	0% (0/1207)	0% (2/1153)	0% (2/1094)	0% (0/490)
% of pts. with severe regurgitation	0% (0/1207)	0% (0/1153)	0% (0/1094)	0% (0/490)

Note: Data reflect transvalvular, paravalvular and indeterminate regurgitation noted at all locations combined.

Table 10: Effectiveness Outcomes, Hemodynamics, Valvular Regurgitation: MVR
All patients analyzed: N=365, percent (numerator/N)

Endpoint	≤30 Days	3-6 Months	1 Year	3 Years
Valvular Regurgitation				
% of pts. with no regurgitation	80% (280/348)	77% (255/331)	77% (206/267)	77% (75/97)
% of pts. with trivial regurgitation	15% (51/348)	15% (51/331)	16% (42/267)	18% (17/97)
% of pts. with mild regurgitation	3% (12/348)	5% (18/331)	5% (13/267)	2% (2/97)
% of pts. with mod regurgitation	1% (5/348)	2% (6/331)	2% (5/267)	1% (1/97)
% of pts. with mod severe regurgitation	0% (0/348)	0% (1/331)	0% (0/267)	2% (2/97)
% of pts. with severe regurgitation	0% (0/348)	0% (0/331)	0% (1/267)	0% (0/97)

Note: Data reflect transvalvular, paravalvular and indeterminate regurgitation noted at all locations combined.

Table 11: Effectiveness Outcomes, Hemodynamics, Mean Pressure Gradient: AVR
All patients analyzed: N=1252, number in subgroup/N, mean ± SD [min., max.]

Endpoint	<30 Days	3-6 Months	1 Year	3 Years
Mean Pressure Gradient (mmHg)				
21 mm	217/240, 14.6 ± 6.5 [2.7, 54.7]	199/240, 13.3 ± 5.3 [3.0, 34.4]	189/240, 14.5 ± 5.3 [2.0, 40.5]	87/240, 15.5 ± 5.6 [4.5, 32.5]
23 mm	456/495, 13.0 ± 5.3 [0.9, 37.0]	446/495, 11.8 ± 4.9 [2.0, 43.1]	425/495, 12.8 ± 5.0 [3.0, 32.7]	198/495, 14.0 ± 5.5 [3.1, 35.5]
25 mm	334/362, 11.6 ± 4.9 [2.0, 32.0]	331/362, 10.6 ± 4.4 [1.1, 35.7]	310/362, 11.8 ± 5.2 [2.0, 38.9]	127/362, 12.1 ± 5.8 [1.4, 43.1]
27 mm	119/130, 11.1 ± 4.1 [2.0, 21.5]	114/130, 9.1 ± 4.0 [2.0, 23.1]	105/130, 10.0 ± 4.0 [3.4, 22.7]	45/130, 10.5 ± 4.1 [3.3, 24.6]
29 mm	24/25, 12.6 ± 5.8 [7.0, 28.8]	21/25, 8.6 ± 2.9 [3.5, 16.8]	21/25, 10.3 ± 2.6 [4.6, 16.0]	16/25, 9.9 ± 2.5 [5.9, 15.1]

Table 12: Effectiveness Outcomes, Hemodynamics, Mean Pressure Gradient: MVR
All patients analyzed: N=365, number in subgroup/N, mean ± SD [min., max.]

Endpoint	<30 Days	3-6 Months	1 Year	3 Years
Mean Pressure Gradient (mmHg)				
25 mm	42/48, 5.9 ± 2.2 [3.0, 13.0]	40/48, 5.5 ± 2.1 [1.0, 12.0]	32/48, 5.6 ± 1.6 [3.0, 9.3]	10/48, 5.1 ± 1.8 [1.9, 8.0]
27 mm	107/115, 5.3 ± 2.2 [2.0, 12.0]	104/115, 4.8 ± 2.1 [1.0, 13.1]	83/115, 4.5 ± 2.2 [1.0, 13.0]	33/115, 4.9 ± 3.0 [1.0, 16.2]
29 mm	133/136, 5.0 ± 2.1 [1.0, 15.0]	125/136, 4.4 ± 2.0 [1.0, 12.5]	101/136, 4.3 ± 1.7 [1.0, 8.6]	36/136, 3.9 ± 1.5 [1.0, 8.3]
31 mm	56/57, 4.7 ± 1.9 [2.0, 10.3]	52/57, 4.1 ± 1.6 [1.0, 7.6]	43/57, 3.7 ± 1.4 [1.0, 6.5]	15/57, 4.0 ± 2.1 [2.0, 9.1]

Table 13: Effectiveness Outcomes, Hemodynamics, Effective Orifice Area: AVR
All patients analyzed: N=1252, number in subgroup/N, mean ± SD [min., max.]

Endpoint	≤30 Days	3-6 Months	1 Year	3 Years
Effective Orifice Area (cm^2)				
21 mm	217/240, 1.4 ± 0.4 [0.6, 3.7]	199/240, 1.4 ± 0.4 [0.7, 3.8]	189/240, 1.3 ± 0.4 [0.6, 3.1]	86/240, 1.3 ± 0.3 [0.7, 2.5]
23 mm	458/495, 1.6 ± 0.5 [0.7, 3.9]	447/495, 1.6 ± 0.5 [0.8, 5.4]	426/495, 1.5 ± 0.4 [0.7, 3.4]	199/495, 1.5 ± 0.4 [0.7, 3.2]
25 mm	336/362, 1.8 ± 0.5 [0.8, 4.2]	331/362, 1.8 ± 0.5 [0.7, 4.0]	311/362, 1.8 ± 0.5 [0.7, 4.2]	127/362, 1.7 ± 0.4 [0.6, 3.0]
27 mm	119/130, 1.9 ± 0.6 [1.0, 4.3]	114/130, 2.0 ± 0.5 [1.0, 3.4]	105/130, 1.9 ± 0.6 [1.1, 3.7]	45/130, 1.9 ± 0.7 [1.0, 4.2]
29 mm	24/25, 2.0 ± 0.5 [1.0, 2.9]	21/25, 2.3 ± 0.6 [1.4, 3.6]	21/25, 2.2 ± 0.7 [1.3, 4.1]	16/25, 2.2 ± 0.6 [1.2, 3.4]

Table 14: Effectiveness Outcomes, Hemodynamics, Effective Orifice Area: MVR
All patients analyzed: N=365 number in subgroup/N, mean ± SD [min., max.]

Endpoint	≤30 Days	3-6 Months	1 Year	3 Years
Effective Orifice Area (cm^2)				
25 mm	39/48, 1.6 ± 0.4 [0.9, 2.9]	36/48, 1.7 ± 0.8 [0.7, 5.6]	27/48, 1.6 ± 0.5 [0.8, 2.3]	7/48, 1.8 ± 0.6 [1.2, 2.8]
27 mm	95/115, 1.7 ± 0.6 [0.8, 4.6]	93/115, 1.7 ± 0.4 [0.9, 2.9]	76/115, 1.7 ± 0.5 [0.7, 3.7]	28/115, 1.6 ± 0.5 [0.3, 3.3]
29 mm	118/136, 1.7 ± 0.5 [0.7, 3.1]	111/136, 1.8 ± 0.5 [0.7, 3.4]	92/136, 1.8 ± 0.5 [0.8, 3.0]	32/136, 1.7 ± 0.5 [1.2, 3.1]
31 mm	53/57, 1.6 ± 0.5 [0.5, 3.0]	47/57, 1.8 ± 0.6 [1.0, 3.1]	37/57, 1.7 ± 0.6 [1.0, 3.2]	14/57, 1.9 ± 0.7 [1.1, 3.8]

10.1 Description of Patients and Analysis for Gender Bias

For AVR, 64% of the patients in the study were male. For MVR, 47% of the patients in the study were male. These proportions of male patients are consistent with the incidence of male patients presenting for aortic and mitral valve replacement in the United States and Canada.

Based on an evaluation of valve-related adverse events, no statistically significant differences were observed in the freedom from valve-related adverse events between men and women for AVR and MVR. Therefore, the results for valve-related adverse events presented in the analyses are representative for both men and women.

Based on an evaluation of mean gradient, effective orifice area, and valvular regurgitation, the hemodynamic performance of the MOSAIC® Porcine Bioprosthesis was similar in men and women for AVR and MVR. Therefore, the hemodynamic results for these parameters presented in the analyses are representative for both men and women.

11. Conclusions Drawn from Studies

The results from the preclinical studies performed on the MOSAIC® Porcine Bioprosthesis for biocompatibility, hydrodynamic performance (steady and pulsatile flow pressure drop, pulsatile and dynamic regurgitation, and flow visualization) and structural performance testing (accelerated wear fatigue, dynamic failure mode, stent creep, stent deflection, and stent absorption/adsorption), suggest that the MOSAIC bioprosthesis is suitable for long-term implant. The MOSAIC bioprosthesis meets specifications for performance.

The acute and chronic animal studies in sheep adequately demonstrated the preclinical *in vivo* safety of the MOSAIC® Porcine bioprosthesis valve.

The clinical study submitted in the PMA submission provides sound scientific evidence that the MOSAIC® Porcine Bioprosthesis is safe and effective for use as a replacement of an impaired aortic or mitral native or prosthetic valve.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risks of illness or injury when used as indicated in accordance with the directions for use.

12. Panel Recommendations

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13. FDA Decision

Based on the reviews of the original PMA application and its amendments, FDA determined that the device provides reasonable assurance of safety and effectiveness when used as indicated in the labeling. FDA found Medtronic Heart Valves manufacturing facility to be in compliance with the Device Quality System Regulation (21 CFR part 820).

14. Approval Specifications

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling.

Postapproval Requirements and Restrictions: See approval order.